

Medical Marijuana: The Risks, Benefits And Medical Implications

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NCNP - Las Vegas, 2017**



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Lets take a minute to contemplate your current thoughts on medical marijuana

Think about the following (write it down now if you can)

- How do you feel about the use of Medical Marijuana?
 - Fan
 - Not a fan
 - I'm not sure how I feel
- Have you had a personal, family member or patient situation in which medical marijuana was used?
 - If so, how was the outcome? Positive, negative, addictive?
- Lets see if you feel the same way at the end of the talk

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- Whenever possible appropriate peer-reviewed studies were used to create the contents of this topic (for which a reference list is provided). However, due to the nature of the subject material, some of the research for this presentation was done using internet searches and non-clinical sites
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Objectives

By the end of this session the participant will be able to:

- Describe medical reasons for using marijuana
- Consider the short term and long term side effects of marijuana
- Discuss the accessibility of medical and recreational marijuana, including the legal and social implications of the drug

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Do you already have an image of a Marijuana User



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Cannabis (Marijuana) The Plant

- Cannabis: 3 sub-species - C. sativa, C. indica and C. ruderalis
- Cannabis sativa (most common) varieties produce marijuana and hemp
- Difference between marijuana and hemp plants = Resin

Marijuana (grown for "high")

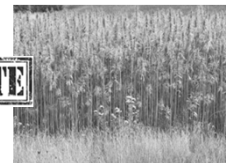
- High resin (rich in trichomes) = High in THC
- Usually grown indoors hydroponically

Hemp for industrial use (No high)

- Low resin = Low in THC
- Grown outside



DEBATE



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Cannabis (Marijuana)

What's in a name?

- The international agreed term is 'cannabis'
- Marijuana is a term used in USA
- Also known as Marijuana, Marihuana, Mariguana:
 - Terms were associated with the Mexican immigrant population (after 1910 Mexican Revolution).
 - Its suggested that the first marijuana laws were aimed at placing social controls on the immigrant population
- Marijuana was spelled marihuana in the Marihuana Tax Act of 1937 and in the Industrial Hemp Farming Act of 2005
 - The Marihuana Tax Act of 1937 criminalized pot possession throughout the United State
 - This tax law passed under the name of Marijuana - medical community did not realize it was cannabis

Street names:

- ☺ Doobie/Dubie
- ☺ Dope
- ☺ Ganga
- ☺ Grass
- ☺ Green
- ☺ Hash
- ☺ Herb
- ☺ Hooch
- ☺ Hydro
- ☺ Joints
- ☺ Marijuana
- ☺ Mary Jane
- ☺ Pot
- ☺ Reefers
- ☺ Smoke
- ☺ Weed

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Cannabis in History

- 8,000-7,000 B.C. the earliest woven fabric apparently was made of hemp fibers
- 2,700 B.C. China ~ used flowers and resin to medically treat menstrual disorders, gout, rheumatism, malaria, constipation, and absent-mindedness
- 1000-2000 B.C. Hemp was used for fiber throughout the world for fabrics
- 1213 B.C. Egyptians used cannabis for treating glaucoma, inflammation and enemas
- 1000 B.C., India and Middle East used a mixture of milk and cannabis (named bhang) as an anesthetic and anti-phlegmatic



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Cannabis in History

- 1840's to 1900's: Cannabis extracts, tinctures and elixirs were 2nd and 3rd most used medicines in America. scientific journals wrote of therapeutic benefits
- 1851: U.S. Pharmacopoeia of Medicines stated cannabis could be used to treat asthma, neuralgia, glaucoma, nausea, epilepsy, depression, rheumatism, arthritis, alcoholism and others.
- Late 1800s British neurologist used cannabis for epilepsy
- 1911: New Orleans ban marijuana (one of the first in US)
- 1937: Banned The Marihuana Tax Act
- 1940's the war effort legalized hemp again (needed hemp ropes and parachutes), but made illegal again post war – when Hemp was imported from India
- 1960's: Rock and Roll – called for legalization again
- 1970's: CBD used for seizures - success but the studies small and not well blinded
- 1996: California legalized marijuana for medical use



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Cannabis - Hemp

- Hemp is bred specifically for:
 - Fiber- paper, fabric, rope, and Construction
 - Seeds – feed, beer, and hemp flour (confections, baking additive)
 - Oil - cooking, nutritional supplements, fuel, paint
- Benefits of Hemp: Typically richer in CBD - Without intoxication
- International Standard:
 - limit of TCH = 0.3% as the official limit for legal hemp
- U.S. law defines hemp as all parts of any *Cannabis Sativa* plant containing no psychoactive properties, except for defined exceptions
- Canadian plant scientists Ernest Small and Arthur Cronquist, wrote 1976 taxonomic report to include hemp and other forms of cannabis
- Of Note: Farm Bill: 2014: President Obama Signed Farm Bill with Amendment to Allow Industrial Hemp Research (adding to legislative/legal confusion)

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Cannabis - Hemp

- 9th century: monks wrote manuscripts, on hemp paper using hemp oil to burn the lamp light
- Medieval times, Islamic physicians used cannabis to treat nausea and vomiting, epilepsy, inflammation, pain, and fever
- Christopher Columbus brought with him gifts of hemp fabrics
- 1620 Mayflower: hemp seeds were brought to USA by pilgrims
- It is said that Thomas Jefferson used hemp paper to draft both
 - The Constitution
 - Declaration of Independence
 - Final documents were written on parchment
- Hemp paper was widely used in that time period
- No evidence has been found/proven regarding the smoking of hemp or marijuana during that time
- Prison uniforms given to slaves from Africa were made from hemp fabric



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Politics Vs Science



- Federal law currently prohibits the use, sale, and possession of marijuana
 - Schedule I – No medical use and not able to be prescribed
- However, many states have legalized marijuana for "medical" use - with an Rx
 - This makes the prescribers responsible for the Rx
 - big responsibility
 - Prescribing a drug that is Schedule I
- Schedule I - Marijuana, heroin, ecstasy and LSD
- Schedule II - cocaine, methamphetamine, opium and morphine

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Politics Vs Science

- Its important to separate the legalization of:
 - Medical marijuana
 - CBD Only
 - Recreational marijuana
- Some states agree to recreational use:
 - Legalized recreational use without a prescription: eg: Colorado, Oregon, Washington State, and Alaska
 - Most recently, California, Maine, Massachusetts, and Nevada all passed measures in November 2016 legalizing recreational marijuana. (Arizona rejected)
- This year Voters in Arkansas, Florida and North Dakota approved legalize medical cannabis

29 Legal Medical Marijuana States and DC
Laws, Fees, and Possession Limits

29 LEGAL MEDICAL MARIJUANA STATES AND DC



http://medicalmarijuana.procon.org/view_resource.php?resourceID=000881 – researched and copied March 2017

Note: on 4/6/17 West Virginia passed a bill making it the **29th state**

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Research Trials



Why is research so limited?

- Lack of Phase 3 clinical trials
- **Schedule I – Controlled Substance**
 - Schedule I status makes it very difficult to use in clinical trials
 - Illegal status scares the research investigators
- Bias may make publication of the work more difficult
- Will trials ever be approved if it includes “smoked” marijuana?
- Until re-scheduled large scale research trials will probably not take place
- Medical and research communities base their opinions on limited studies, possible side effects, and “opinions” on personal or anecdotal patient experiences

Cartoon from: <http://www.marijuana.com/blog/news/2014/10/novelist-patricia-cornwell-donates-500k-for-harvard-marijuana-research/>

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Cannabinoids

Endocannabinoids – refer to natural cannabinoids in the body

- Intercellular lipid messengers that activate the cannabinoid receptors - similar to neurotransmitters like acetylcholine or dopamine
- Endocannabinoids are lipophilic molecules and not very soluble in water
- Receptors - CB₁ (brain) and CB₂ (immune system). These receptors exist in the parts of the brain that control N/V, chronic pain and seizures

Phytocannabinoids – refer to the molecules derived from the cannabis plant

- Naturally found in varieties of cannabis plants - concentrated in the resin
- Produced in structures known as glandular trichomes
- Cannabis contains multiple cannabinoids (60-80), but little is known about most
- The most studied cannabinoids are: Tetrahydrocannabinol (THC) and cannabidiol (CBD)

Synthetic cannabinoids - are those which have been man-made (Rx or chemical)

- Manufactured artificially to mimic the effects of natural cannabinoids
- Medications: Dronabinol (Marinol) and Nabilone (Cesamet)
- K2 and Spice

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Cannabinoids

Phytocannabinoids

Tetrahydrocannabinol (THC) - psychoactive “high” effect (Δ8THC and Δ9THC)

- Mostly associated with Marijuana (flower/bud)
- Positive effects: analgesic, anti-spasmodic, anti-tremor, anti-inflammatory, appetite stimulant and anti-emetic properties,

Cannabidiol (CBD) - medical effects without making the subject “high”

- CBC is mostly associated with hemp, but is best sourced from CBD-rich cannabis plants
- Positive effects: anti-inflammatory, anti-convulsant, anti-psychotic, anti-oxidant, neuroprotective and immunomodulatory effects

Cannabinol (CBN) – trace amounts - psychoactive, sedative and analgesic

- Both **THC and CBD** are used in “medical marijuana”
- Separately or combined “**Ratio is important**”
- Choices of cannabinoid depends on individual needs, the medical marijuana laws, and the prescribing provider

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Cannabis (Marijuana) The Plant

Cannabis: 3 sub-species –

- Cannabis Sativa
 - Most popular for smoking
 - Used for industrial hemp
 - Tall – up to 15 feet
 - Usually dried
 - High ratio of THC to CBD
- Cannabis Indica
 - 3-6 feet tall and able to be grown indoors
 - Flowers are stickier and resin makes hashish
 - More sedative
 - Higher in CBN than other varieties
- Cannabis Ruderalis
 - Small/short plant (20-25 inches)
 - Not very psychotropic
 - Mostly used by breeders and cultivators



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Medical Marijuana

- American Academy of Neurology (represents over 27,000 neurologists) became one of the first medical organizations in the U.S. to endorse the use of medical marijuana
- They issued guidelines saying that oral cannabis, medical marijuana pills and medical marijuana spray may help ease pain and other symptoms caused by MS
- They do not yet endorse smoked marijuana
- Difference between current Rx “marijuana” pharmaceutical and medical marijuana
 - Rx approved in USA uses synthetic THC
 - Medical marijuana is natural but not FDA approved.
- There are no safety/purity standards, limited clinical trials and remains Schedule I – sometimes leaving the prescriber with questions
- FDA approved THC in the USA
 - **Dronabinol (Marinol) – Schedule III**
 - **Nabilone (Cesamet) – Schedule II**

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Prescription Cannabinoid

Dronabinol (Marinol) - Schedule III - (Synthetic delta-9-THC)

Approved Indication:

- Anorexia associated with weight loss in HIV/AIDS
- Chemotherapy-induced nausea and vomiting



Side effects:

- CNS (reported by 33% of patients)
- Tachycardia, palpitations, orthostatic hypotension, Nausea, Vomiting and diarrhea
- Confusion, dizziness, drowsiness, depression, hallucinations and conjunctival injection (red eyes)

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Prescription Cannabinoid

Nabilone (Cesamet) - Schedule II - (Synthetic delta-9-THC)

Approved Indication:

- Nausea and vomiting related to chemotherapy
- Side Effects:
 - Drowsiness, spinning sensation, dry mouth,
 - Feeling "high", lack of coordination, mood changes, difficulties concentrating, headache
 - Tachycardia and hypotension.
 - Mental side effects may last 2-3 days
 - Adverse psychiatric reactions can persist for 48 to 72 hours following cessation of treatment



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New Prescription Cannabinoid

New medications: Both are on the Fast Track for FDA approval – but not currently approved for use in the U.S. for any condition (www.GWPharm.com)

Nabiximols (Sativex) – oro-mucosal spray (vaporizer/Spray)

- Composed primarily of two cannabinoids: CBD and THC
- Moderate to severe multiple sclerosis spasticity (MSS)
- Approved in 25 countries – including Canada, Europe, Scandinavia and UK
- Canada also allows Sativex to be used for neuropathic pain and advanced cancer pain
- GW Pharmaceuticals is collaborating with Otsuka Pharmaceutical on Phase III clinical trials for cancer pain - but no regulatory application has been made for MS spasticity



Epidiolex - oral solution of pure plant-derived cannabidiol (CBD only)

- For treatment for severe childhood epileptic conditions: Dravet syndrome, Lennox-Gastaut Syndrome, Tuberous Sclerosis Complex and Infantile Spasms
 - Epidiolex was granted fast-track status and is in late stage trials following positive early results from the drug
- GW Pharmaceuticals is seeking FDA approval to market under the tradename Epidiolex

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FDA Approved Vs Legislative Approved

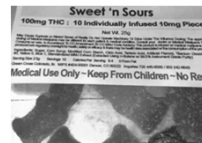
What if approved prescription medications are not the best option for your patient, or they have too many side effects...what options do you have?

Do you consider marijuana products?

Depends on the State

Consider State vs federal approval

Consider FDA vs DEA vs legislation



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Marijuana - Cannabinoids

Δ9-Tetrahydrocannabinol (THC)

- Psychoactive ingredient
- Anticonvulsant, but can also be pro-convulsant
- The psychotropic effects of Δ⁹-THC limit tolerability, and are the reason many use it for recreation
- Marijuana's therapeutic effects (versus side effects) depend on the concentration of THC
- Cannabidiol (CBD) has an ability to mitigate the psychoactive effects of THC. As a result, the THC-CBD ratio for many strains of marijuana has been engineered to achieve desired effects (Hill, 2015)
- However, some evidence suggests CBD may reduce clearance of THC and increase effect/time of THC activity

Cannabidiol (CBD)

- Non-psychoactive ingredient
- Neuroprotective and anti-inflammatory and anticonvulsant
- Well tolerated (Devinsky, et al 2014)

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Cannabis Classification and THC

United Nations Office on Drugs and Crime (UNODC) states:

- Cannabis flower often contains 5% THC
- Cannabis resin can contain up to 20% THC content
- Cannabis oil (solvent extraction) may contain more than 60% THC content (not used in medicine and not to be confused with CBD oil)

Cannabis is more potent now than ever

- THC content in marijuana had increased worldwide from 1970 to 2009 (Cascini, Aiello, & Di Tanna, March 2012)

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Cannabis Preparations Containing THC

- Herbal** - Marijuana describe the dried flowers, leaves and stems of the female cannabis plant, which are usually smoked and are least potent of the preparations. Usually 3%-20% THC and considered recreational more than medicinal.
 - Industrial hemp plants contain less than 1% THC and are thus not valued for recreational use
- Hashish** - made from the resin (a secreted gum) of the cannabis plant. It is dried and pressed into small blocks, and smoked (eg: crumbled into tobacco) or added to food, consumed orally or smoked, and is also vaporized
- Hash oil** - most potent cannabis product, is a thick oil obtained from hashish and is usually smoked. Produced by solvent extraction-Cannabinoids: THC (~ 30%) and THCA (~ 60%)
 - New trend in street drug use known as Dab, Wax and butane honey oil.



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Cannabis (Marijuana) Preparations

- Tincture** - dried flowers of the female cannabis plant are soaked in ethanol to create a solvent. The THC and other cannabinoids dissolve into the alcohol. Consumed sublingually, orally, sublingual spray, or topically (eg: Green Dragon)
- Kief** - is a powder, rich in resin trichomes (high THC concentration) and usually consumed as a powder or compressed to produce cakes of hashish. From the colloquial Arabic كَيْف *kāf/kīf*, meaning pleasure or intoxication.
- Infusion** - mixed with non-volatile solvents such as butter or cooking oil
- Cannabis preparations are more bioavailable when prepared or infused in an oil, such as butter



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Cannabis (Marijuana) Preparations

- Cannabis Liquor** - Liquor may be infused with cannabinoids. Best to cook stems and leaves into brandy or rum. Can be added to coffee and other beverages.
- Cannabis Topicals (applied to the skin)** - Cannabinoids combined with a penetrating topical cream can enter the skin and body tissues and allow for direct application to affected areas (e.g. allergic skin reactions, post-herpes neuralgia, muscle strain, inflammation, swelling, etc.). Less or limited psychoactive affect



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Cannabis (CBD) Preparations

- CBD Oil** is the most common preparation
 - Oral or sub-lingual
 - Intranasal
 - Transdermal (patches) and balm or lotion
 - Capsules (made from oil)
- Past centuries (especially 1800's) was used for gout, rheumatism, malaria, pain, and fever.
- Non-psychoactive
- However, as a component of the cannabis/marijuana plant it is a Schedule I substance under the federal Controlled Substances Act (CSA)
- Most well known use is Charlotte's Webb – used for Refractory epilepsy—especially in children with Dravet syndrome



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Parents Continue Fight To Legalize Marijuana Oil In CT To Treat Seizures



Charlotte's mother Paige crossed state lines from Connecticut to Colorado to purchase the CBD oil

Charlotte was having seizures every 30 minutes and was in hospice care

Charlotte, now 9, doesn't speak but enjoys life.

She can walk, ride a bike and she goes to school

Now has about two seizures per month

Charlotte Figi, who has epilepsy, was given a marijuana-based oil named Charlotte's Web that her mother believes reduced her seizures. (Courtesy of Paige Figi)

By SARAH CODY Special to The Courant

<http://www.courant.com/features/hc-mommy-minute-0118-20160114-story.html>
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Charlotte's Web

- Charlotte's web - marketed as dietary supplements and claim efficacy against Dravet Syndrome
- Charlotte's Web was developed in 2011 by the Stanley brothers – through crossbreeding a strain of marijuana with industrial hemp
 - Less THC and more CBD – in 2014 THC content was 0.3%
 - Sometimes referred to as "Realm Oil"
- A number of high profile and anecdotal reports have sparked debate
- Dravet syndrome (rare) catastrophic form of intractable epilepsy that begins in infancy



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CBD Legal Status

- **CBD Is Legally Allowed in 47 States**
 - 29 states allow medical marijuana
 - 18 states have CBD-only laws
 - Nebraska has pending legislation
 - 3 states remain illegal Idaho, South Dakota, and Kansas
 - North Carolina and Wisconsin have additional legislation for medical marijuana pending

Note: Legislation changes regularly.
Please check the laws of your own state

18 States have CBD-only laws

- Alabama (2014)
- Delaware (2015)
- Florida (2014)
- Georgia (2015)
- Indiana (2017)
- Iowa (2014)
- Kentucky (2014)
- Mississippi (2014)
- Missouri (2014)
- North Carolina (2014)
- Oklahoma (2015)
- South Carolina (2014)
- Tennessee (2014)
- Texas (2015)
- Utah (2014)
- Virginia (2015)
- Wisconsin (2014)
- Wyoming (2015)

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CBD Legal Status

- December 2016: DEA ruled that all extracts from a cannabis plant are Schedule I substances. ALL cannabinoids (to include CBD) were part of this newly established drug code under the Controlled Substances Act (CSA).
 - Currently challenged by hemp and CBD oil producers
 - Industrial hemp laws enacted under the 2014 US Farm Bill makes hemp legal – therefore excluded from DEA rule
 - March 2017: DEA backed off position – stating CBD is legal if it comes from a legal part of the cannabis plant (eg: mature stalk)
 - However, farmers say it is difficult to extract CBD from stalk where hemp fibers are taken
- Hempseed oil is federally legal, but not legally the same thing as CBD oil, and does not always contain pure CBD
 - Only 4 states mandate purity and potency testing of marijuana product: Colorado, Washington, Oregon, and Alaska

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Cannabidiol (CBD) Indications


- Epilepsy/Seizures – reduced frequency
 - Especially in treatment-resistant epilepsy in children and young adults
- Huntington's disease
- Cancer – of multiple types and multiple symptoms
- Neuropsychiatric disorders
 - Anxiety
 - Post traumatic stress disorder
 - Schizophrenia or schizophreniform disorder
 - Autism and mental health conditions
 - Psychosis - May have anti-psychotic effects – insufficient evidence - inconclusive
- Neonatal hypoxic-ischemic encephalopathy

Many studies, including Devinsky 2014 & 2016

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Cannabidiol (CBD) Indications


- HIV-associated neuropathic pain
- Spasms and pain
- Spasms associated with multiple sclerosis
- Dystonia
- Dystonia in Parkinson's disease
- Parkinson's disease with psychotic symptoms
- Anti-inflammatory effects
- Dependency and withdrawal of cannabis
 - May be used BID to treat marijuana withdrawal symptoms – reduce or eliminate anxiety or dissociative symptoms
 - Studies are limited
 - Not enough basic pharmacologic data on the role of CBD, especially in the treatment of refractory epilepsy. (Welty, 2014)




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CBD and THC Combination

- THC to CBD Ratio:
 - Balance is the Key
- Studies are limited
 - Most have used whole cannabis - not measured or broken down into THC or CBD
- It appears that CBD may protect against some of the psychological effects of TCH
- Studies using a combination of CBD and THC for Multiple sclerosis have little to no adverse effects on cognition or mood – other than those observed with similar psychoactive drugs





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Indications of Cannabis

- Nausea and vomiting
- Appetite loss and weight loss
 - Usually HIV/AIDS – anorexia and wasting syndrome
- GI inflammation and maybe Crohn's
- Hiccups
- Chronic Pain
- Neuropathic pain
 - Pain associated with MS, HIV and traumatic or spinal injury
- Multiple sclerosis
 - Reduced pain
 - Reduced spasticity
 - May improve urinary symptoms
- Epilepsy
 - Mixed results. Pediatrics seem to reduce seizures by 50% (Press et al, 2015)
 - Adults may not (Hamerle et al 2014)
- Headaches

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Indications of Cannabis

- Inflammation
- Psychiatric:
 - Bipolar disorders PTSD
 - Anxiety
- Glaucoma – IOC reduced - most likely THC rather than CBD (studies are old 1970-80's)
 - New studies needed.
 - Effective dose is frequent and high = ↑ side effects
- May assist with:
 - Reduced alcohol use
 - Reduced opioid consumption
 - Assisting in opiate withdrawal symptoms
 - Quit cocaine
- Cannabis may be addictive – But CBD may assist in cannabis withdrawal

Spontaneous regression of benign brain tumor may have been associated with cannabis use (Foroughi et al, 2011)

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Multiple sclerosis, epilepsy, and movement disorders

A systematic review of medical marijuana by an AAN subcommittee

Looked at: oral cannabis extract (OCE) containing THC and CBD, Tetrahydrocannabinol (THC), Nabiximols and smoked marijuana

- **Spasticity:** OCE, THC, and nabiximols appear to be **effective** (not in USA)
- **Central pain or painful spasms:** OCE, THC and nabiximols are **probably effective**
- **Urinary dysfunction:** nabiximols is **probably effective** for reducing bladder voids/day; THC and OCE are probably not
- **Tremor:** THC, OCE and nabiximols are **probably ineffective** at treating tremors, or levodopa-induced dyskinesias in patients with Parkinson disease.
- Unknown efficacy in epilepsy or other movement disorders: non-chorea-related symptoms of Huntington disease, Tourette syndrome, and cervical dystonia
- Risk of serious adverse psychopathologic effects was nearly 1%
- Smoked marijuana is of unclear efficacy for reducing pain

(Koppel, et al 2014)

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American Academy of Neurology

- The AAN: concluded that certain forms of medical marijuana (only in pill or oral spray form) can help treat some symptoms of MS
- These include spasticity, certain types of pain (pain related to spasticity, including painful spasms, and painful burning and numbness) and overactive bladder.
- Most of the MS studies examined pill or oral spray forms of medical marijuana.
- The AAN caution that medical marijuana can worsen thinking and memory problems which many people with MS suffer from these problems already due to the disease itself

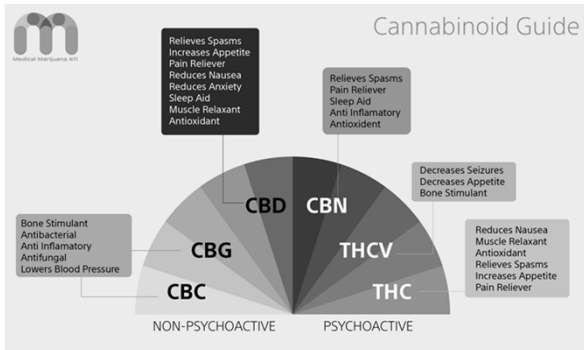
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American Academy of Neurology

- The American Academy of Neurology concluded that there is not enough information to show if medical marijuana (smoked or medical marijuana) is safe or effective in these neurologic diseases:
 - Motor symptoms in Huntington's disease
 - Tics in Tourette syndrome
 - Cervical dystonia (abnormal neck movements)
 - Seizures in epilepsy
- Parkinson's disease: medical marijuana does not help relieve abnormal movements that can develop in the late stages of the disease from the drug levodopa, which is the main drug used to treat shaking, stiffness and slowness of movements.

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Balancing Cannabinoid with Indication for Use



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How do you feel about dosing?



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Dosing THC

- Dosing difficult – Limited studies (anecdotal)
- Start low – Go slow -
Titrate to effect and side effects
 - 5-10mg 2-4 times a day
 - 1 to 3 g/day when smoked or vaporized
 - 25 mg of pharmaceutical-grade cannabis with a THC (content 9.4%) was effective in reducing intensity of pain, improved sleep and was well tolerated when smoked as a single inhalation 3x/day for five days (Ware, 2010)
- To treat eating disorders, 7.5-30mgs of THC by mouth daily for four weeks
- A dose of 15-30mgs of cannabis extract capsules has been taken by mouth in five-milligram increments, based on tolerance, for 14 days
- Multiple sclerosis symptoms: Cannabis plant extracts containing 2.5-120 milligrams of a THC-CBD combination by mouth daily for 2-15 weeks

Strength of Cannabis (assuming negligible cannabidiol)	Daily dosage of cannabis corresponding to 2.5 - 90 mg of THC
10% THC	.15 g - 5.55g
15% THC	.12 g - 3.69g
20% THC	.08 g - 2.79g
25% THC	.04 g - 2.25g
30% THC	.01 g - 1.86g

Donald Abrams, MD, Professor of Clinical Medicine at the University of California, San Francisco, et al (2004)

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Dosing

- Acceptable dose:
 - Most recommend serving size is 10mg of THC per serving
- Edibles are easily over dosed
 - Eg: Chocolate bars and cookies
- Example: These Kief chips
 - Small print on the bottom 120mg
 - 12 chips per bag
 - No instruction to just eat one
 - No website, 800 number or warnings on the bag



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Pharmacokinetics of THC

Inhaled Route: THC bioavailability (smoked) averages 30%

- Maximum plasma concentration of THC occurs within minutes
- Psychotropic effects start within seconds, max after 15–30 minutes, and taper off within 2–3 hours

Oral Ingestion: THC bioavailability (oral) approximately 4-12%

- Psychotropic effects are delayed by 30–90 minutes, reach max after 2–3 hours and last for about 4–12 hours, depending on dose
- Oral absorption is highly variable
- The onset of action is delayed making titration of dosing more difficult

Distribution and Elimination:

- THC is widely distributed, particularly to fatty tissues.
- The spleen and body fat are long-term storage sites
- The elimination of THC and its many metabolites (from all routes) occurs via the feces and urine. Metabolites persist in the urine and feces for several weeks.

- (Merrick, J., et al, 2016). (McGilveray, I. J., 2004). (Grotenhermen, F. 2003).

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Dosing CBD



- Titrate to effect, but may take 3-4 weeks
- Increasing dosage every 3-4 weeks by 5-25mg until symptom relief
- Sleep disorders, 40-160 milligrams of CBD has been taken by mouth
- Chronic pain: 2.5-20 mg CBD by mouth for an average of 25 days
- Epilepsy: 200-300 mg of CBD by mouth daily for up to 4.5 months
- Huntington's disease: 10 mg per kilogram of CBD by mouth daily for six weeks
- Schizophrenia: 40-1,280 mg CBD by mouth daily for up to four weeks
- CBD is well tolerated in humans with doses up to 600 mg and Does not result in psychotic symptoms (Mechoulam, 1978)

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Pharmacokinetics of CBD

- Bioavailability varies greatly depending on route of administration of CBD
 - 34%-46% for intranasal administration (Paudel et al, 2010)
 - 40% for vaporization (Solowij et al, 2014)
 - Oral CBD may be as low as 6%, owing to significant first-pass metabolism (Hawksworth et al, 2004)
- Orally administered cannabidiol (CBD) has shown a relatively high incidence of somnolence in a pediatric population in recent studies. The acidic environment of normal gastrointestinal fluid converts CBD into the psychoactive components Δ^9 -THC and Δ^8 -THC (Merrick et al, 2016)
- Cannabidiol can both inactivate and enhance various cytochrome P450 enzymes
- CBD is a more potent inhibitor of cytochrome P450 enzymes than grapefruit
 - CBD reduces the enzymatic degradation of warfarin, thereby increasing its duration of action and effect.
 - A person taking a CBD-rich product may have changes in INR, and warfarin dose may be difficult to stabilize

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General Side Effects of Marijuana

- Nausea, vomiting
- Dizziness or fainting symptoms
- Seizure
- Increased weakness, fatigue and feelings of intoxication (Koppel, 2014)
- Increased risk of ischemic stroke (Singh, 2012)
 - Mixed information about strokes, appear to be ↑ risk with ↑THC and ↑ reports with synthetic cannabinoid (Spice)
- There may be increased risk of testicular cancer (Huang, 2015)
- Marijuana smokers over 40yrs have higher odds of a clinical diagnosis of glaucoma, rather than self-reported glaucoma in order to gain Rx. Possible explanation is that marijuana use actually may increase glaucomatous optic nerve damage (Baker et al 2015)

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Behavioral Side Effects

- Behavioral or mood changes
- Anxiety, panic, and attentional abnormalities
- Cognitive impairment
- Psychosis
- Suicidal thoughts or hallucinations
- Mood changes and suicidal thoughts are of concern in MS, who are at an increased risk for depression or suicide (1% of population)
- Psychosis, dysphoria, and anxiety are associated with higher concentrations of THC (Koppel, 2014)
- 5 Year follow-up of cannabis users had higher level of psychotic symptoms and lower level of functioning (Clausen, et al, 2014)
- Cannabis may induce paranoia and disorientation in novice users
- Sexual behavior: small amounts may increase desire and arousal in both genders. Large amounts cause ED in males (Agabio et al, 2016)



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Cardiovascular Side Effects

- Tachycardia and increased cardiac output
- THC = vasoconstrictor effect and cardiac ischemia due to ↑ cardiac workload and postural hypotension (Karabag et al, 2015)
- Increased blood carboxyhemoglobin levels = inadequate myocardial blood supply (Karabag et al, 2015)
- Vasovagal Syncope, increased vagal tone, sinus bradycardia, hypotension, sinus arrest and asystole (Brancheau, et al, 2016)
- Trigger acute coronary syndromes (ACS), cardiac arrhythmias, sudden death, atrial fibrillation, asystole, and may ↑ risk of strokes (Rezkalla, 2016) – however, many times marijuana was used with tobacco, so effects may be related to tobacco
- Case studies
 - 26yr male - ACS and acute renal failure (Karabag et al, 2015)
 - 33yr male - MI (Renard et al, 2012)
 - 40yr male - ACS related to multi-vessel coronary artery (Filali et al, 2013)
 - 18yr male - Prolonged atrial fibrillation with normal heart structure precipitated by new-onset seizures (Singh, et al 2014)

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Pulmonary Side Effects

- Lung function abnormalities are different from those of tobacco smoking
- Large airway inflammation, bronchitis and effects bronchial mucosa
- Increased large airways resistance
- Lung Hyperinflation
- Reports of bullous emphysema
- No convincing evidence that it causes COPD or emphysema
- Risk of lung cancer – debatable – evidence is mixed, some say ↑ 2-fold
- Methods of inhaling cannabis (joint, bong, pipe or vaporizer) are still unknown
- Cannabis has acute bronchodilator effects but there is no evidence that this is clinically useful
- Difficult to separate tobacco and marijuana as the causation



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Table 1. Adverse Effects of Short-Term Use and Long-Term or Heavy Use of Marijuana.

Effects of short-term use

Impaired short-term memory, making it difficult to learn and to retain information

Impaired motor coordination, interfering with driving skills and increasing the risk of injuries

Altered judgment, increasing the risk of sexual behaviors that facilitate the transmission of sexually transmitted diseases

In high doses, paranoia and psychosis

Effects of long-term or heavy use

Addiction (in about 9% of users overall, 17% of those who begin use in adolescence, and 25 to 50% of those who are daily users)*

Altered brain development*

Poor educational outcome, with increased likelihood of dropping out of school*

Cognitive impairment, with lower IQ among those who were frequent users during adolescence*

Diminished life satisfaction and achievement (determined on the basis of subjective and objective measures as compared with such ratings in the general population)*

Symptoms of chronic bronchitis

Increased risk of chronic psychosis disorders (including schizophrenia) in persons with a predisposition to such disorders

* The effect is strongly associated with initial marijuana use early in adolescence.

Adverse effects related to regular use of marijuana during adolescence

Volkow et al, 2014

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Side Effects of Cannabidiol (CBD)

- Most studies report CBD is well tolerated
- No** psychomotor or psychoactive effects
- No** changes in HR, BP or temperature, NO EKG or EEG changes
- No** GI effects
- Chronic use and high doses up to 1,500 mg/day of CBD are reportedly well tolerated in humans
- Immune system - effects may be generally positive.
- May** worsen HIV infection, tumor genesis, metastases or allergic inflammation in the lungs

However: May alter drug pharmacokinetics and pharmacodynamics

- Inhibition of hepatic drug metabolism - Inactivate human P450 3A4
 - Opiates, benzodiazepines, macrolide antibiotics, CCB some statins, and more
- Decreased activities of p-glycoprotein and other drug transporters
 - Bergamaschi, 2011

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Ongoing CBD Research

- The NIH recognizes the need for additional research on the therapeutic effects of CBD and other cannabinoids, and supports ongoing efforts to reduce barriers to research in this area.
- NIH is currently supporting a number of studies on the therapeutic effects as well as the health risks of cannabinoids.
- These include studies of the therapeutic value of CBD for:
 - Treatment of substance use disorders (opioids, alcohol, cannabis, methamphetamine)
 - Attenuation of the cognitive deficits caused by THC
 - Neuropathic pain due to spinal cord injury
 - Mitigating the impact of cannabis use on risk for schizophrenia
 - Examination of the potential of CBD as an antiepileptic treatment

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Withdrawal from Cannabis (THC)

- Sleep disturbances and insomnia and trouble falling asleep
- Unpleasant dreams
- Loss of appetite
- Increased anxiety
- Feeling bored
- Feeling sad or depressed
- Migraine
- Irritability and restlessness
- Craving for cannabis



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- Mice who were only given a placebo displayed natural age-dependent learning and memory losses
- Mice treated with cannabis were just as good as the two-month-old control animals
- "The treatment completely reversed the loss of performance in the old animals," reported Prof. Andreas Zimmer

- A chronic low dose of delta9-tetrahydrocannabinol (THC) restores cognitive function in old mice, *Nature Medicine*, DOI: 10.1038/nm.4311

- https://www.eurkalet.org/pub_releases/2017-05/ueb-cra050817.php

PUBLIC RELEASE: 8 MAY 2017

Cannabis reverses aging processes in the brain

Researchers at the University of Bonn restore the memory performance of Methuselah mice to a juvenile stage

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Memory performance decreases with increasing age. Cannabis can reverse these aging processes in the brain. This was shown in mice by scientists at the University of Bonn with their colleagues at The Hebrew University of Jerusalem (Israel). Old animals were able to regress to the state of two-month-old mice with a prolonged low-dose treatment with a cannabis active ingredient. This opens up new options, for instance, when it comes to treating dementia. The results are now presented in the journal *Nature Medicine*.



Like any other organ, our brain ages. As a result, cognitive ability also decreases with increasing age. This can be noticed, for instance, in that it becomes more difficult to learn new things or devote attention to several things at the same time. This process is normal, but can also promote dementia. Researchers have long been looking for ways to slow down or even reverse this process.

Scientists at the University of Bonn and The Hebrew University of Jerusalem (Israel) have now achieved this in mice. These animals have a relatively short life expectancy in nature and

BMBS: PROF. DR. ANDREAS ZIMMER (LEFT) AND THE NORTH-RHINE-WESTPHALIA SCIENCES MINISTER BEREN SCHULEZ (CENTER) ARE IN THE LAB OF THE INSTITUTE OF MOLECULAR PSYCHIATRY AT UNIVERSITY OF BONN. View more +

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The New York Times

- March 27th, 2017
- Los Angeles drug rehabilitation clinic named High Sobriety
- Uses marijuana as a treatment for heroin addiction
- Rather than being a gateway into drugs, could it be a gateway out

● <https://www.nytimes.com>

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Implications in Pregnancy

- THC crosses the placenta rapidly, but its major metabolite does not
- Marijuana can remain in the body for up to 30 days = prolonging fetal exposure
- Smoking marijuana = 5 x the amount of carbon monoxide as cigarette smoking (perhaps altering fetal oxygenation)
- Marijuana alters brain neurotransmitters and brain biochemistry
- There may be subtle abnormalities in infant neurobehavior related to prenatal marijuana exposure
- No significant effects on fetal growth, congenital anomalies, or withdrawal
- Long-term studies = affects on behavior, cognition, and achievement but not on language or growth (Behnke et al, 2013)
- Mixed reports on low birth weights, seems to correlate with tobacco use
- May increase risk for NICU admission (Warshak et al, 2015)

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Social Implications of Long Term use and Increased Accessibility of the drug

- Regular use of cannabis, or using cannabis from earlier ages, increases risk of:
 - Lower levels of educational attainment
 - Welfare dependence and unemployment
 - Using other, more dangerous illicit drugs
 - Psychotic symptomatology
- Of note, a substantial proportion of regular adult users do not experience harmful consequences as a result of cannabis use (Fergusson et al, 2015)
- Repeated exposure to cannabis during adolescence may have detrimental effects on brain
 - Resting functional connectivity
 - Intelligence
 - Cognitive function
- A Longitudinal Study (Camchong, 2016)

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Social Implications of Long Term use and Increased Accessibility of the drug

- Medical marijuana use could impact driver safety
 - reflecting marijuana's disruptive effects on motor coordination and time perception (Volkow, 2015)
- Marijuana use by adolescents is more prevalent in states that passed a medical marijuana law (Hasin et al, 2015)
- The epidemiological literature in the past 20 years shows that cannabis use increases the risk of accidents and can produce dependence
- There are consistent associations between regular cannabis use and poor psychosocial outcomes and mental health in adulthood (Hill, 2015)

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Legal Marijuana Ends at Airport Security, Even if It's Rarely Stopped

By JACQUE WELLS APRIL 18, 2017



The singer Melissa Etheridge in Nashville before a performance last month. She uses medical marijuana for pain relief from breast cancer treatment and has kept it in checked luggage with a doctor's recommendation attached. www.nytimes.com

Traveling with Marijuana can be a challenge – even if it was legally prescribed

<http://www.nytimes.com/>

People in 29 states can legally use medical marijuana for a variety of problems, including the relief of pain, anxiety or stress. But what if they want to travel with it?

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Which U.S. States Accept Out-of-State Medical Marijuana Authorizations?

As more and more states legalize medical marijuana, a lot of patients are starting to wonder if their authorizations are valid in any states other than where they were first issued. Fortunately, some medical marijuana-legal states do indeed accept out-of-state authorizations, and they're listed below. The number of states is small right now, but we'll continue to update it as more states start to allow out-of-state documentation.*

*Please note: Accepting an out-of-state medical marijuana authorization is entirely up to the discretion of a dispensary owner, particularly in stricter states like Michigan and Rhode Island. We recommend calling in advance to ensure that they will allow you to purchase medicine.

(Updated 8/29/2017)

Arizona	Hawaii	Maine
Michigan	Nevada	New Hampshire
Pennsylvania	Rhode Island	

<https://www.leafly.com/news/cannabis-101/which-us-states-accept-out-of-state-medical-marijuana-authorization>

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Possession limits per state: <http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881>

State	Year Passed	How Passed	Possession Limit
Marijuana State Laws – Summary Chart from ProCon.org			
Alaska	1998	Ballot Measure # 5 (58%)	1 oz usable; 6 plants (3 mature, 3 immature)
Arizona	2010	Proposition 203 (50.3%)	2.5 oz usable; 12 plants
Arkansas	2016	Ballot Measure Issue # 5 (52.2%)	3 oz usable per 14-day period
California	1996	Proposition 215 (56%)	8 oz usable; 6 mature or 12 immature plants
Colorado	2000	Ballot Amendment 20 (54%)	2 oz usable; 6 plants (3 mature, 3 immature)
Connecticut	2012	House Bill 5389 (66.5% H, 53.1% S)	2.5 oz usable
Delaware	2011	Senate Bill 137 (27.14% H, 17.4% S)	6 oz usable
Florida	2016	Ballot Amendment 2 (71.3%)	Amount to be determined
Hawaii	2000	Senate Bill 643 (20.34% H, 39.42% S)	4 oz usable; 7 plants
Illinois	2013	House Bill 1 (51.57% H, 35.21% S)	2.5 ounces of usable cannabis during a period of 14 days
Maine	1999	Ballot Question 2 (61%)	2.5 oz usable; 6 plants
Maryland	2014	House Bill 881 (25.11% H, 44.2% S)	30-day supply; amount to be determined
Massachusetts	2012	Ballot Question 3 (69%)	60-day supply for personal medical use (10 oz)
Michigan	2008	Proposal 1 (63%)	2.5 oz usable; 12 plants
Minnesota	2014	Senate Bill 2470 (46.15% H, 69.40% S)	30-day supply of non-smokable marijuana
Montana	2004	Initiative 148 (52%)	1 oz usable; 4 plants (mature); 12 seedlings
Nevada	2000	Ballot Question 9 (68%)	2.5 oz usable; 12 plants
New Hampshire	2013	House Bill 573 (28.44% H, 18.4% S)	Two ounces of usable cannabis during a 10-day period
New Jersey	2010	Senate Bill 110 (48.18% H, 25.93% S)	2 oz usable
New Mexico	2007	Senate Bill 523 (36.31% H, 32.3% S)	6 oz usable; 18 plants (4 mature, 12 immature)
New York	2014	Assembly Bill 6387 (17.11% H, 49.18% S)	30-day supply non-smokable marijuana
North Dakota	2016	Ballot Measure 5 (63.7%)	7 oz per 14-day period
Ohio	2016	House Bill 523 (71.24% H, 18.15% S)	Maximum of a 90-day supply; amount to be determined
Oregon	1998	Ballot Measure 47 (55%)	24 oz usable; 24 plants (6 mature, 18 immature)
Pennsylvania	2016	Senate Bill 3 (149.44% H, 42.7% S)	30-day supply
Rhode Island	2006	Senate Bill 0710 (20.10% H, 30.1% S)	2.5 oz usable; 12 plants
Vermont	2004	Senate Bill 76 (22.71% H, 64.92% S)	2 oz usable; 9 plants (2 mature, 7 immature)
Washington	1998	Initiative 592 (59%)	8 oz usable; 6 plants
Washington, DC	2010	Amendment act 818-022 (104.99%)	2 oz dried
West Virginia	2017	Senate Bill 385 (74.24% H, 38.4% S)	30-day supply (amount TBD)
Marijuana State Laws – Summary Chart from ProCon.org			

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Everyone is Watching Colorado

Colorado has had 17 years of medical-marijuana legalization and now recreational legalization

Early identification of trends

- Created surveillance systems to monitor the numbers of ED visits and hospitalizations related to marijuana use
- Data on calls to poison-control centers
- Proposed regulations would ensure that products are easily separable into single servings containing no more than 10 mg of THC
- Public health officials also launched a public awareness campaign about safe storage of marijuana products and child-resistant packaging in January 2015. (Ghosh, et al 2015)
- October 2016 - 60 Minutes on CBS – Highlights Problems After Marijuana Legalization in Colorado
 - Interview a Dr. LaPook who supports a ban of marijuana in his county
 - Positive THC in newborns and teens

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Patient Education

- Considerations: Driving or operating machinery
- Being aware of the metabolism and how marijuana completes for the same pathways as many medications. This may affect medications requiring balance: eg: warfarin, digoxin and levothyroxine
- Educate on signs of addiction
 - Needing the drug
 - Lack of control over the amount being used
 - Spending increased amount of time using or attaining the drug
 - Negatively affects relationships or work
 - Neglecting appearance or responsibilities
- Be aware of potential side effects – especially cardiac
- Safe storage: Keep cannabis away from children in a child proof locked area
- Mixing with tobacco or smoking: consider second hand smoke

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In Conclusion

- There is a difference between recreational and medicinal use
- All Marijuana products are Schedule I and the therefore illegal
 - DEA now states that CBD is legal if it is derived from a lawful part of the plant
 - DEA has not yet stated that it is legal if sourced from industrial hemp
- Marijuana is a continued battle in legislation, political arenas and the court of public opinion and its effects may be felt throughout Healthcare
- You don't have to take a stance, you simply have to care for your patient ~ Continue to put your patients needs first
- Focus on evidence based practice
- Find out your state legislation/rulings, and stay informed

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Now that we have reviewed some information about the use of Medical Marijuana – Lets find out you're opinions

Has your opinion changed? (Did you write it down earlier?)

How do you feel about the use of Medical Marijuana?

- I'm a Fan
- I don't like it
- I'm not sure how I feel
- It's a little more clear
- I need more information
- I'm indifferent - I might be asleep!

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- Questions
- Contact: Andreaefre@yahoo.com
- Please contact me for the extensive reference list for further reading. Also of interest, see:
 - WAMM: The Wo/Men's Alliance for Medical Marijuana - Santa Cruz, California
 - Weed Grandma Shows Us How to 420 Braise It
 - <https://www.youtube.com/watch?v=Z2Xd7cseGcE>

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